Medical and Pediatric Oncology 26:230–237 (1996)

Late Cardiotoxicity After Treatment for a Malignant Bone Tumor

A. Postma, MD, M.T.E. Bink-Boelkens, MD, G.C.M. Beaufort-Krol, MD, R.A.M. Kengen, MD, N.J. Elzenga, MD, M.J.M. Schasfoort-van Leeuwen, RN, H. Schraffordt Koops, MD, and W.A. Kamps, MD

Cardiac function was assessed in long-term survivors of malignant bone tumors who were treated according to Rosen's T_5 or T_{10} protocol, both including doxorubicin. Thirty-one patients, ages 10–45 years (median age 17.8 years) were evaluated 2.3–14.1 years (median 8.9 years) following completion of treatment. Cumulative doses of doxorubicin were 225–550 mg/m^2 (median dose 360). The evaluation consisted of a history, physical examination, electrocardiogram (ECG), signal averaged ECG, 24-hour ambulatory ECG, echocardiography and radionuclide angiography. Eighteen of 31 (58%) patients showed cardiac toxicity, defined as having one or more of the following abnormalities: late potentials, complex ventricular arrhythmias, left ventricular dilatation, decreased shortening fraction, or decreased ejection fraction. The incidence of cardiac abnormalities increased with length of follow-up ($P \leq .05$). No correlation could be demonstrated between cumulative dose of doxorubicin and cardiac status, except for heart rate variability. When adjusted to body surface area, the left ventricular posterior wall thickness (LVPW index) was decreased in all patients. The incidence of doxorubicin-induced cardiotoxicity is high and increases with follow-up, irrespective of cumulative dose. Life-long cardiac follow-up in these patients is warranted. The results of our study suggest that heart rate variability and LVPW index could be sensitive indicators for cardiotoxicity.

Key words: Anthracyclines, cardiotoxicity, long-term effects

INTRODUCTION

The anthracycline derivatives doxorubicin and daunorubicin are among the most effective agents in the combined modality treatment of pediatric malignancies, including bone tumours. Their use is limited by dose-related cardiotoxicity. Although the acute and early manifestations of anthracycline- induced cardiotoxicity have been well recognized, an alarmingly high incidence of late cardiac effects in asymptomatic patients was published recently [1–3].

Among the factors that could potentiate anthracycline-related cardiac damage are a high cumulative dose, a young age or an advanced age at the time of treatment, pre-existing cardiac disease, previous irradiation of the chest wall, and concurrent use of cyclophosphamide [3–5]. In addition, doxorubicin may be more cardiotoxic than daunorubicin [6]. Most studies of late cardiac toxicity refer to study populations that are more or less heterogeneous with respect to treatment-related risk factors such as mediastinal irradiation, use of daunorubicin and/or doxorubicin, cumulative dose of anthracyclines, and concurrent use of cyclophosphamide in a subgroup of the patients [2,7]. We therefore evaluated the cardiac status of long-term survivors of a malignant bone tumour who were uniformly treated according to two consecutive, largely corresponding protocols, based on Rosen's T_5 and T_{10} protocols [8,9]. The anthracycline derivative used in both chemotherapy regimens was doxorubicin; the cumulative dose was $\leq$550 mg/m^2. All patients received cyclophosphamide, and none had mediastinal irradiation.

PATIENTS AND METHODS

Patients

Between 1977 and 1990, 41 patients with osteosarcoma and seven patients with malignant fibrous histiocytoma of bone were treated according to the Rosen protocols [8,9]. Before 1979 chemotherapy was based on the T_5 protocol, and from 1979 the T_{10} approach was used. In

Departments of Pediatric Oncology (A.P., W.A.K.), Pediatric Cardiology (M.T.E.B.-B., G.C.M.B.-K., N.J.E., M.J.M.S.L.), Nuclear Medicine (R.A.M.K.), and Surgical Oncology (H.S.K.), University of Groningen, Groningen, The Netherlands.

Received August 8, 1994; accepted January 29, 1995.

Address reprint requests to A. Postma, University Hospital Groningen, Dept. of Pediatric Oncology, P.O. Box 30.001, 9700 RB Groningen, The Netherlands.

both protocols doxorubicin was given intravenously as bolus injection on 3 consecutive days; dosages were 30, 30, and 15 mg/m^2 (max. 550 mg/m^2) in the T_5 protocol and 3 × 20 mg/m^2 (maximum dose 450 mg/m^2) in the T_{10} protocol. Total duration of exposition to doxorubicin was 6–9 months. Cyclophosphamide was administered intravenously in bolus doses of 1,200 mg/m^2 in T_5 and in doses of 600 mg/m^2 on 2 consecutive days in T_{10}; administration of cyclophosphamide was followed by aggressive hydration.

Nine patients died from metastatic disease. None of them had evidence of congestive heart failure (CHF) prior to their death. One patient died from cardiac failure; she had developed CHF within 2 months after completion of 550 mg/m^2 doxorubicin; after a symptom-free interval of 10 years her heart function deteriorated rapidly. One patient died suddenly during ice-skating 5 years off-therapy (no autopsy was performed). Three patients were lost to follow-up. Two patients refused, and one was excluded because of pregnancy. The 31 patients who participated in the study had no evidence of malignant disease and were 2.3–14.1 years (median 8.9) off chemotherapy.

Methods

The evaluation consisted of a history, physical examination, electrocardiogram (ECG), signal averaged ECG (SAECG), 24-hour ambulatory ECG, 2D, M-mode and colour Doppler echocardiography, and radionuclide angiography (RNA) for measurement of the left ventricular ejection fraction (LVEF). As most patients had orthopaedic impairment resulting from an amputation or limb salvage surgery of the lower extremity, no exercise testing was performed. For the detection of late potentials a SAECG was obtained using the arrhythmia research technology (ART) model 1200EPX (Austin, TX). Ventricular late potentials are low-amplitude, high-frequency signals at the end of the QRS complex, which are thought to represent delayed depolarisation of viable myocardium that alternates with fibrotic tissue [10,11]. The SAECG was recorded from standard bipolar X, Y, and Z leads. At least 200 beats were averaged with a noise level below 1.0 μV and filtered with a bidirectional filter of 25–250 Hz and 40–250 Hz. Three parameters were measured: the total duration of the filtered QRS complex (tQRS), the duration of low-amplitude signals (below 40 μV) in the terminal part of the QRS complex (LAS), and the root mean square voltage of the last 40 ms of the QRS complex (RMS40). The presence of late potentials was defined according to the criteria of the task force committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology [10].

The 24-hour ambulatory ECG was analysed by a Marquette Laser XP system for arrhythmias, ST segment, and heart rate variability (Marquette HRV software version). Spectral and non-spectral analysis of heart rate variability were performed. High (0.15–0.40 Hz) and low frequencies (0.04–0.15 Hz) were expressed as a percentage of total frequency (0.01–1.00 Hz). Ventricular arrhythmias were classified according to the Lown's criteria [12]. Lown 4 was considered abnormal. Ventricular tachycardia is defined as a series of three or more repetitive excitations which originate from the ventricle, with a rate faster than 120/min. Two-dimensional, M-mode and colour Doppler echocardiography were performed by a single observer (M.S.v.L.) to exclude interobserver variability and included measurement of left ventricular posterior wall (LVPW) both at end-systole and at end-diastole, left ventricular internal dimension at end systole (LVIDes) and at end diastole (LVIDed), and shortening fraction (SF). The relative LVPW thickness was calculated as LVPWes/LVIDes [13]. Normal mean value is 0.52 ± 0.05. The value for LVPWed was adjusted for body surface area (LVPW index) [3]. Left ventricular function obtained by echocardiography was considered abnormal if the SF was <0.29 or if the LVID (es or ed) was $\geq$95th percentile [14].

Left ventricular ejection fraction (LVEF) was measured with equilibrium gated radionuclide angiography (RNA). ECG-gated RNA was performed with 300 MBq Tc-99m-labelled autologous red blood cells which were labelled in vivo after pretinning. Acquisition was done with a large-field-of-view gamma-camera equipped with a low-energy all-purpose parallel-hole collimator in a position in which left and right ventricles were separated optimally (mostly lao 30–45 dg). Acquisition time was 12 min. The data were stored in a dedicated computer system (PDP11-33, gamma 11), and the LVEF was calculated with a semi-automatic software program. RNA was considered abnormal if the LVEF was $<55\%$.

A poor nutritional status has been reported to affect tolerance to chemotherapy [15]; therefore, maximum weight loss during chemotherapy was calculated as a percentage of initial body weight (for amputees: weight after amputation). Previous cardiac studies (during or at the completion of chemotherapy) had only been done in a subset of patients. Therefore, earlier results, if available, were not included in the evaluation. The correlation of the results of cardiac evaluation with age at diagnosis, length of follow-up, and cumulative dose of doxorubicin was examined. To be able to consider possibly potentiating factors, dosages of cyclophosphamide and weight loss during chemotherapy were evaluated as well. Because of the small numbers in each patient group we did not analyse the influence of tumour localisation, histology, or type of surgery on the results of the cardiac evaluation.

Electrocardiographic changes and arrhythmias as a manifestation of acute cardiotoxicity are generally considered to be transient and of little clinical significance [16]. However chronic electrocardiographic changes and

TABLE I. Characteristics of 31 Patients Treated for a Malignant Bone Tumor*

	Total	Normal 13	Abnormal[a] 18	P value[b]
Male	23	11	12	NS
Female	8	2	6	NS
Age at diagnosis (med., yrs)	17.8	18.3	16.7	NS
(range)	(10–45.8)	(14.3–38.5)	(10–45.8)	
Follow-up (med., yrs)	8.9	6	9.2	<.05
(range)	(2.3–14.1)	(2.3–12.7)	(3.3–14.1)	
DOX cum. (med., mg/m^2)	360	360	360	NS[c]
(range)	(225–550)	(225–550)	(240–550)	
Cyclo cum (med., mg/m^2)	4800	4800	4800	NS
(range)	(500–9,600)	(500–9,600)	(2,400–9,600)	
Weight loss (med., % of initial body weight)	8	7	10	NS
(range)	(0–22)	(0–22)	(9–19)	
CHF at completion of treatment	3	0	3	NS

*Total and subgroups with normal or abnormal cardiac function.
cum, cumulative; DOX, Doxorubicin; cyclo, cyclophosphamide; CHF, congestive heart failure.
[a]Definition of abnormal cardiac function: one or more of the following symptoms; LP, ventricular arrhythmias (Lown 4), LVID es ≥ 95th percentile, LVID ed ≥ 95th percentile SF <0.29, LVEF < 55%.
[b]Student's *t*-test.
[c]Except for HRV, see text.

late arrhythmias may reflect injury to myocardial cells, as does left ventricular dysfunction. Therefore cardiotoxicity was defined as having one or more of the following abnormalities: late potentials, complex ventricular arrhythmias (Lown 4), LVID es ≥ 95th percentile, LVID ed ≥ 95th percentile, SF < 0.29, EF < 55%.

Statistical analysis was performed by two-tailed Student *t*-test, X^2 test, and Fisher exact test. A *P* value of ≤ .05 was considered significant.

RESULTS

Characteristics of the 31 patients that participated in the study are shown in Table I. Owing to severe chemotherapy-related toxicity, nine of these patients had premature termination of all treatment (cardiac toxicity 4, renal impairment 4, infection 1). Three out of the four patients with early cardiac toxicity had CHF after completion of 550 mg/m^2 doxorubicin; one was asymptomatic but a progressive decrease of the shortening fraction after a cumulative dose of 300 mg/m^2 doxorubicin was diagnosed echocardiographically. The results of the present cardiac evaluation are summarized in Table II. Clinical symptoms (fatigue and/or palpitations) were mentioned by six patients (19%). One of them had physical signs of CHF; she was one of the patients who had premature termination of chemotherapy because of cardiac toxicity and for the last 13 years she has suffered from recurrent cardiac failure.

ECG

A prolonged QTc interval > 0.44 seconds was seen in one patient, abnormally flattened T waves in five patients (16%), and ST segment elevation in one patient.

Signal Averaged ECG

Late potentials were detected in four patients (13%). There was no relation between late potentials and the presence of ventricular arrhythmias or ventricular dysfunction. None of the patients with CHF at completion of treatment had late potentials.

24-Hour ambulatory ECG

Ten patients had no ventricular arrhythmias, three had sporadic uniform premature ventricular contractions (PVCs) (Lown 1), ten had sporadic multiform PVCs (Lown 3), six had ventricular couplets (Lown 4A), and two had non-sustained ventricular tachycardia (Lown 4B). Non-sustained supraventricular tachycardia was found in two, and couplets of premature atrial contractions were seen in seven patients. The incidence of complex ventricular arrhythmias increased with length of follow-up (1/10 patients with follow-up 2–6 years, 5/10 patients with follow-up 10–15 years, *P* = .05) (Fig. 1). Spectral analysis of heart rate variability (HRV) showed significantly more low frequency (mainly sympathetic activity) and less high frequency (respiratory modulation by parasympathetic activity) in patients treated with ≥400 mg/m^2 doxorubicin compared with <400 mg/m^2. Non-spectral analysis showed significantly less heart rate

TABLE II. Results of Late Cardiac Evaluation in 31 Patients Treated for a Malignant Bone Tumour*

Patient	Sex	Age at diagnosis[a]	Follow-up since last doxorubicin	Late potentials	Lown 4	SF < 0.29	LVIDes ⩾ p95	LVIDed ⩾ p95	Rel. LVPW < 0.42	LVPW index < 6.3 mm	EF < 55%
1	M	10.8	4.3	−	+	−	+	−	+	+	−
2	M	35.9	6.4	−	−	−	−	−	+	+	−
3	M	10	9.2	−	+	+	−	−	+	+	−
4	M	14.3	11.2	−	+	−	−	−	+	+	−
5	M	14.3	2.3	−	−	−	−	−	+	+	−
6	M	17	5.3	−	−	−	−	−	+	+	−
7	M	20.6	8.8	−	−	−	−	−	+	+	−
8	M	38.5	6	−	−	−	−	−	+	+	−
9	M	27.9	4	−	−	−	−	−	+	+	−
10	M	11.8	8.9	+	−	−	−	−	+	+	−
11	F	27.6	7.7	−	−	+	+	+	+	+	+
12	F	35.1	12.1	−	+	−	−	−	+	+	−
13	M	20.1	3.8	+	−	+	−	−	+	+	+
14	M	13.5	9	+	−	+	−	−	+	+	−
15	F	15.3	2.4	−	−	−	−	−	+	+	−
16	M	14.3	9.4	−	−	−	−	−	+	+	−
17	M	23.1	5.8	−	−	−	−	−	+	+	−
18	M	43.4	9.2	−	−	−	−	−	−	+	+
19	M	26.9	3.2	−	−	−	−	−	+	+	−
20	F	15.8	8.2	−	+	−	−	−	−	+	−
21	M	12	12.5	−	−	+	−	−	+	+	−
22	M	17.3	9.1	−	−	−	−	−	+	+	−
23	F	14.3	13.1	−	+	+	−	−	+	+	−
24	F	45.8	13	−	+	+	+	+	+	+	+
25	F	12.4	13.1	−	+	−	+	−	+	+	−
26	M	18.3	12.7	−	−	−	−	−	+	+	−
27	M	21.3	4.3	+	−	−	−	−	−	+	−
28	M	17.6	11.3	−	−	+	+	−	+	+	=
29	M	19.3	5.6	−	−	−	−	−	+	+	+
30	F	17.1	11.6	−	−	−	−	−	+	+	−
31	M	20	14.1	−	−	−	+	−	+	+	−
Total no. abnormal				4	8	8	6	2	28	31	5

*SF, shortening fraction; LVID, left ventricular internal diameter; es, end systolic; ed, end diastolic; p95, 95th percentile; rel., relative; LVPW, left ventricular posterior wall; EF, ejection fraction. + abnormal, − normal.

[a]Years.

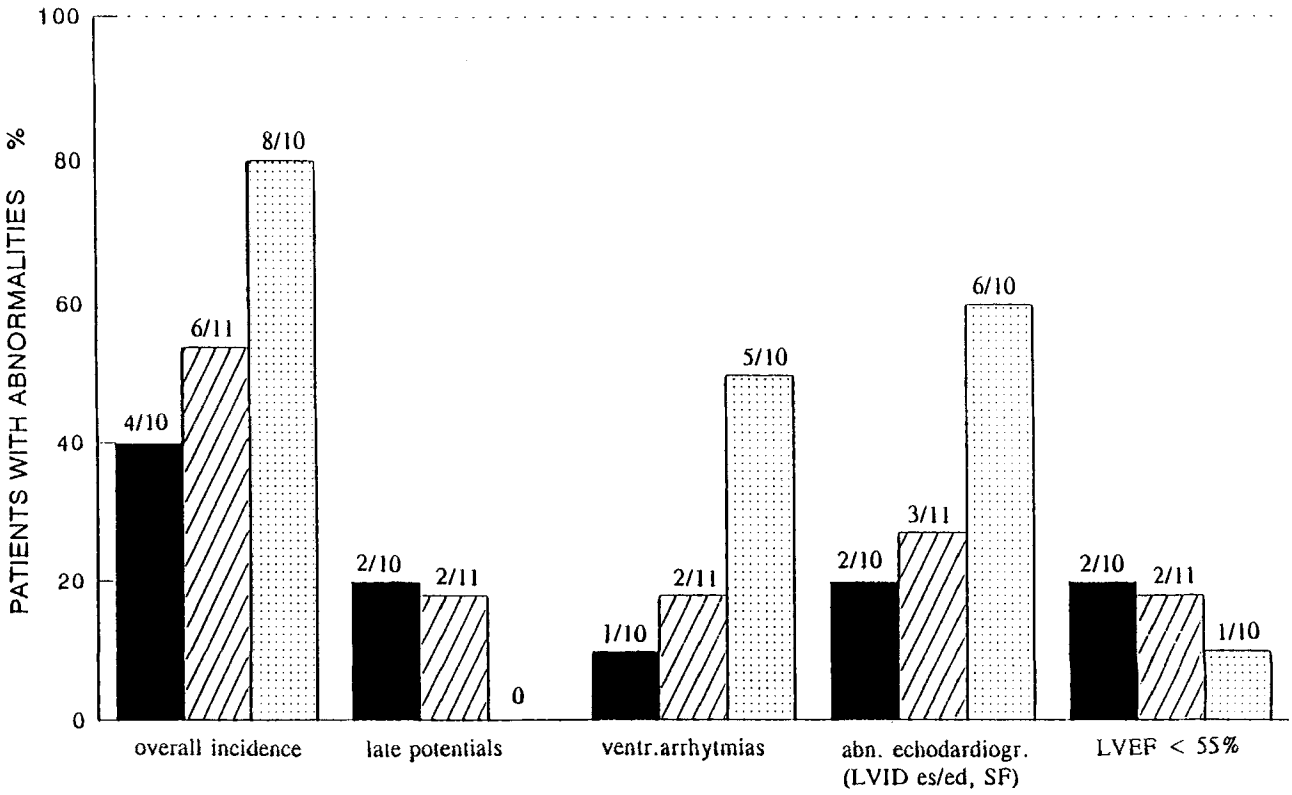

Fig. 1. Relation of cardiotoxicity and length of follow-up in 31 patients with malignant bone tumors. Years of follow-up: Solid bars, 2–6 (n = 10); hatched bars, 6–10 (n = 11); stippled bars, 10–15 (n = 10).

TABLE III. Relation Between Heart Rate Variability and Dose of Doxorubicin in 31 Patients With Malignant Bone Tumors*

Heart rate variability	DOX < 400 mg/m^2	DOX ≥ 400 mg/m^2	*P* value
SDRR (ms)	197 ± 70	141 ± 46	<.02
pNN50 (%)	17.2 ± 10.5	6.5 ± 4.8	<.001
LF (%)	0.67 ± 0.03	0.7 ± 0.04	<.05
HF (%)	0.40 ± 0.09	0.33 ± 0.1	<.05
LF/HF ratio	1.74 ± 0.46	2.33 ± 0.79	<.05

*DOX, doxorubicin; HF, high frequency; LF, low frequency; SDRR, standard deviation about the mean RR interval; pNN50, proportion of adjacent RRs more than 50 ms different. Values are expressed as mean ± SD.

variability (especially SDRR and pNN50) in the group treated with ≥400 mg/m^2 (Table III).

Echocardiography

Eleven patients (35%) had abnormal findings on echocardiography. Left ventricular shortening fraction was <0.29 in eight patients (26%). LVIDes was ≥95th percentile in six patients (19%); two of them demonstrated LVIDed ≥95th percentile as well. The incidence of abnormal SF and/or left ventricular dilatation increased with length of follow-up; 2/10 patients with follow-up 2–6 years and 6/10 patients with follow-up 10–15 years ($.05 < P < .1$) (Fig. 1). The relative LVPW thickness was <0.42 in 28 patients (90%) and <0.37 in 19 patients (65%). LVPW index was 0.43 ± 0.04 cm/m^2, which was significantly decreased in all 31 patients if compared with the values in normal persons (0.81 ± 0.09 cm/m^2, $P < .0001$) found by Lipshultz et al. [3]. In three patients there was evidence of mitral valve incompetence, in two cases of mild degree and in one case of moderate degree.

Radionuclide Angiography

In five patients (16%) the LVEF was <55%. Patients with abnormal resting ejection fraction more frequently had left ventricular dilatation ($P < .01$). Cardiotoxicity

was demonstrated in 18 patients (58%) including the three patients who developed CHF at the end of chemotherapy. If late potentials were not regarded as a sign of cardiotoxicity, the number of patients with abnormal function was 16 (52%). No abnormalities were found in the patient who had premature termination of chemotherapy after progressive decrease of SF.

Neither the prevalence of abnormal cardiac function nor the individual abnormalities showed a correlation with sex, age at diagnosis, weight loss during chemotherapy, or dosages of cyclophosphamide and doxorubicin, even if the patients who were treated according to the T_5 protocol, who had more cyclophosphamide, were left out of the analysis. But patients with abnormal cardiac function had a significant longer follow-up than patients with normal results (median 6 vs. 9.2 years, $P < .05$) (Table I). There especially was a relation between long-term follow-up and ventricular arrhythmias or abnormalities on echocardiography, but not between length of follow-up and late potentials or LVEF <55% (Fig. 1).

DISCUSSION

Cardiac abnormalities, defined as late potentials, ventricular arrhythmias, left ventricular dilatation, decreased SF, or decreased LVEF, were demonstrated in 18/31 (58%) patients 2.3–14.1 years after discontinuation of treatment with doxorubicin. However 12 of these 18 patients are (still) asymptomatic. The incidence of cardiac abnormalities increased with length of follow-up. If late potentials were excluded from the evaluation, the number of patients with abnormal cardiac function was 16 (52%), and the correlation between any abnormality and length of follow-up was significant: 3/10 patients with follow-up 2–6 years showed abnormal cardiac function versus 8/10 patients with follow-up >10 years ($P < .05$).

According to the chemotherapy protocol the range between minimum and maximum dose of doxorubicin was small. So, as we had expected, no correlation could be demonstrated between cumulative dose of doxorubicin and cardiotoxicity except for a significant decrease of heart rate variability for higher doses of doxorubicin. A cumulative dose as low as 240 mg/m^2 did not preclude cardiotoxicity (Table I).

Patients with longer follow-up have received more cyclophosphamide, as in the T_5 protocol the cumulative dose of cyclophosphamide was higher. This may have aggravated the incidence of cardiotoxicity, although the doses used remained below the level considered cardiotoxic. Cyclophosphamide-induced cardiotoxicity is supposed to be related to high doses as used preparatory to bone marrow transplantation (200 mg/kg/dose), and there is no evidence of cumulative cardiac damage after repeated moderate doses of cyclophosphamide [17–19]. However until now little is known about cyclophosphamide-induced late cardiac effects.

Some authors indicate that young age at diagnosis (<4 years) is a risk factor for anthracycline-induced cardiomyopathy [3]. Age was not a prognostic factor within the present study group, but in our study the youngest patient was already 10 years of age at the time of treatment. The failure to identify associations between patient or treatment variables except for length of follow-up may be related to the small number of subjects evaluated, rather than true lack of an association.

ECG and Signal-Averaged ECG

A prolonged QTc interval has been considered as an early sign of ventricular dysfunction [7,20]. This could not be affirmed by our data. Late potentials are correlated with the presence of fragmented electrical activity, due to inhomogenous propagation of conduction in scarred myocardium. Recent studies have supported the value of the SAECG for risk stratification after myocardial infarction, especially in relation to the development and inducibility of ventricular arrhythmias [11]. We found an incidence of 13% late potentials similar to 15% in our earlier study [21]. As we could not find any relation with cumulative dose, occurrence of ventricular arrhythmias, or ventricular dysfunction, the meaning of late potentials in this patient group remains unclear.

24-Hour Ambulatory ECG

Potentially serious ventricular arrhythmias were detected in eight patients (26%), irrespective of cumulative doses of doxorubicin. This is in agreement with the results of Larsen et al. [7], who found ventricular ectopy in patients with cumulative doses of anthracyclines of >200 mg/m^2. The relation between ventricular arrhythmias and cardiac arrest is well known. Sudden death in patients several years after completion of chemotherapy with anthracyclines has been described [2]. The sudden death of one of our own asymptomatic patients may have been due to arrhythmia. Neurohumoral modulation of cardiovascular function is an important component of the hemodynamic alterations in patients with CHF. Analysis of HRV is a non-invasive method of investigating the autonomic control of the heart. A diminished vagal but relatively preserved sympathetic modulation is found in chronic CHF and after myocardial infarction. After myocardial infarction a diminished HRV is associated with an increased risk of mortality [22,23]. Heart rate variability was significantly impaired in patients who received ≥400 mg/m^2 doxorubicin and was the only parameter showing a correlation with cumulative dose. Similar results were reported by Hrushesky et al. [24], who found that diminished respiratory sinus arrhythmia predicted congestive heart failure during treatment with doxorubicin. This suggests that HRV could be a sensitive index for cardiotoxicity.

Echocardiography

Echocardiographically left ventricular dilatation and/or diminished shortening fraction was detected in 35% of the patients. However, 90% showed a decreased relative LVPW thickness, and the LVPW index was below normal in all patients and even lower than in the patients described by Lipshultz et al. [3], suggesting substantial loss of myocytes and consequent dilatation and elevated wall stress. Lipshultz hypothesized that an age less than 4 years at treatment is a predictive factor for cardiac dysfunction because of impairment of myocardial growth. In our study group most patients were at the age of puberty or older and had almost completed somatic growth at the time of treatment. The incidence of measurable cardiac toxicity increased with the duration of follow-up, which endorses Steinherz' conception that doxorubicin treatment at any age is responsible for myocardial cell death and fibrosis, and that this is progressive even after cessation of treatment [2]. Long-term sequential follow-up of patients is needed to confirm this assumption. Long- term follow-up is all the more important as recently evidence was found that heart failure could be prevented by early treatment of asymptomatic patients with reduced left ventricular ejection fraction [25].

Radionuclide Angiography

RNA has proven to be useful for serial monitoring of LVEF during treatment with anthracyclines [26,27]. In our study RNA was not a sensitive method for detection of cardiotoxicity, as LVEF was decreased in only 5/31 (16%) patients, with the overall incidence of cardiotoxicity being 58%. In addition this technique has the disadvantage of using radioisotopes. Therefore, we do not recommend RNA for follow-up of young patients off-treatment.

CONCLUSIONS

We conclude that there is an alarmingly high incidence of doxorubicin-induced cardiotoxicity, even after cumulative doses that were previously considered "safe." This incidence of cardiotoxicity increases with length of follow-up. Therefore, patients need prolonged, probably life-long cardiac follow-up with close attention to signs of cardiac failure. As there especially was a relation between length of follow-up and the incidence of ventricular arrhythmias and/or echocardiographic abnormalities, we recommend 24-hour ambulatory ECG and echocardiography for evaluation of late cardiotoxicity. The results of our study suggest that heart rate variability and left ventricular posterior wall thickness adjusted for body surface could be sensitive indices of cardiotoxicity.

ACKNOWLEDGMENTS

The authors are indebted to Mrs. R.J. Schilperoort for secretarial help.

REFERENCES

1. Goorin AM, Chauvenet AR, Perez-Atayde AR, Cruz J, Mckone R, Lipshultz SE: Initial congestive heart failure, six to ten years after doxorubicin chemotherapy for childhood cancer. J Pediatr 116:144–147, 1990.
2. Steinherz LJ, Steinherz P, Tan CTC, Heller G, Murphy ML: Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 266:1672–1677, 1991.
3. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP: Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 324: 808–815, 1991.
4. Dresdale A, Bonow RO, Wesley R, Palmeri ST, Barr L, Mathison D, D'Angelo T, Rosenberg SA: Prospective evaluation of doxorubicin-induced cardiomyopathy resulting from post surgical adjuvant treatment of patients with soft tissue sarcomas. Cancer 52: 51–60, 1983.
5. Minow RA, Benjamin RS, Lee ET, Gottlieb JA: Adriamycin cardiomyopathy—risk factors. Cancer 39:1397–1402, 1977.
6. Myers CE, Chabner BA: Anthracyclines. In Chabner BA, Collins JE (eds): "Cancer Chemotherapy, Principles and Practice." Philadelphia: J.B. Lippincott, 1990, pp. 356–381.
7. Larsen RL, Jakacki RI, Vetter VL, Meadows AT, Silber JH, Barber G: Electro cardiographic changes and arrhythmias after cancer therapy in children and young adults. Am J Cardiol 70:73–77, 1992.
8. Rosen G, Murphy ML, Huvos AG, Gutierrez M, Marcove RC: Chemotherapy en bloc resection and prosthetic bone replacement in the treatment of osteogenic sarcoma. Cancer 37:1–11, 1976.
9. Rosen G, Caparros B, Huvos AG, Kosloff C, Nirenberg A, Cacavio A, Marcove RC, Lane JM, Mehta B, Urban C: Pre-operative chemotherapy for osteogenic sarcoma. Cancer 49:1221–1230, 1982.
10. Breithardt G, Cain ME, Ee-sherif N, Flowers NC, Hombach V, Janse M, Simson MB, Steinbeck G: Standards for analysis of ventricular late potentials using high-resolution or signal-averaged electrocardiography: a statement by a task force committee of the European Society of Cardiology, the American Heart Association and the American College of Cardiology. J Am Coll Cardiol 17:999–1006, 1991.
11. Gomes JA, Winters SL, Ip J: Signal averaging of the surface QRS complex: practical applications. J Cardiovasc Electrophysiol 2:316–330, 1991.
12. Lown B, Wolf M: Approaches to sudden death from coronary heart disease. Circulation 44:130–142, 1971.
13. Bennett DH, Evains DW, Rai MVJ: Echoardiographoc left ventricular dimensions in pressure and volume overload. Their use in assessing aortic stenosis. Br Heart J 37:971–977, 1975.
14. Daniels O, Voogd PJ, Gussenhoven WJ, De Knecht S, Rijsterborgh H, Van Lier H: Left ventricular inner dimensions in normal children. In Sobotka MA (ed): "Anthracycline Cardiotoxicity in children; an echocardiographic study." Thesis State University Leiden, The Netherlands, 1991, pp 97–100.
15. Van Eys J: Malnutrition in pediatric oncology. In Newell GR, Ellison NM (eds): "Nutrition and Cancer: Etiology and Treatment." New York: Raven Press, 1981, pp. 411–429.
16. Von Hoff DD, Rozencweig M, Piccart M: The cardiotoxicity of anticancer agents. Semin Oncol 9:23–33, 1982.
17. Colvin M, Chabner BA: Alkylating Agents. In: Chabner BA,

Collins JM (eds: "Cancer Chemotherapy, Principles and Practice." Philadelphia: J.B. Lippincott, 1990, pp. 276–313.
18. Goldberg M, Antin JH, Guinan EC, Rappeport JM: Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. Blood 68:1114–1118, 1986.
19. Braverman AC, Antin JH, Plappert MT, Cook EF, Lee RT: Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. J Clin Oncol 9:1215–1223, 1991.
20. Schwartz CL, Hobbie WL, Truesdell S, Constine LC, Clark EB: Corrected QT interval prolongation in anthracycline-treated survivors of childhood cancer. J Clin Oncol 11:1906–1910, 1993.
21. Tamminga RYJ, Bink-Boelkens MTE, Kievit J: Ventricular late potentials: another expression of cardiotoxicity of cytostatic drugs in children? Int J Cardiol 36:283–288, 1992.
22. Saul JP, Arai Y, Berger RD, Lilly LS, Colucci WS, Cohen RJ: Assessment of autonomic regulation in chronic congestive heart failure by heart spectral analysis. Am J Cardiol 61:1292–1299, 1988.
23. Kleiger RE, Miller JP, Bigger JT, Moss AJ: and the Multicenter post-infarction research group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59:256–262, 1987.
24. Hrushesky WJM, Fader DJ, Berestka JS, Sommer M, Hayes J, Cope FO: Diminishment of respiratory sinus arrhythmia foreshadows doxorubicin-induced cardiomyopathy. Circulation 84:697–707, 1991.
25. The SOLVD Investigators: Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction. N Engl J Med 327:685–691, 1992.
26. Schwartz RG, McKenzie WB, Alexander J, Sager P, D'Souze A, Manatunga A, Schwartz PE, Berger HJ, Setaro J, Surking L, Wackers FJT, Zaret BL: Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Am J Med 82:1109–1118, 1987.
27. Wiles HB: Nuclear Cardiology. In Garson A., Bricker JT, McNamara DG (eds): "The Science and Practice of Pediatric Cardiology." Philadelphia: Lea and Febiger, 1990, pp. 836–851.